EXHIBIT A

EXPERT REPORT

DAVID A. KESSLER, M.D.

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I. QUALIFICATIONS

1. My name is David A. Kessler, M.D. I received my M.D. degree from Harvard Medical School in 1979 and my J.D. degree from the University of Chicago Law School in 1978.

2. I did my pediatrics training at Johns Hopkins Hospital.

3. I was appointed in 1990 by President George H. W. Bush as Commissioner of the United States Food and Drug Administration and was confirmed by the United States Senate. I also served in that position under President William Jefferson Clinton until February 1997.

4. I have taught food and drug law at Columbia University Law School, and I have testified many times before the United States Congress on food, drug, and consumer protection issues under federal and state law. Over the last thirty years, I have published numerous articles in legal, medical, and scientific journals on the federal regulation of food, drugs, and medical devices. I have had special training in pharmacoepidemiology at Johns Hopkins Hospital. My resume is included as Appendix A. A list of cases in which I have appeared as a witness in the last four years, and documentation of my expert witness fee, is attached as Appendix B. A list of materials reviewed or relied upon is attached as Appendix C.

5. As Commissioner, I had ultimate responsibility for implementing and enforcing the United States Food, Drug, and Cosmetic Act (the "Act"). I was responsible for overseeing five Centers within FDA. They included, among others, the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health and the Center for Biologics Evaluation and Research. In addition to those duties, I placed high priority on getting promising therapies for serious and life-threatening diseases to patients as quickly as possible. During my tenure as Commissioner, the FDA announced a number

of new programs including: the regulation of the marketing and sale of tobacco products to children; nutrition labeling for food; user fees for drugs and biologics; preventive controls to improve food safety; measures to strengthen the nation's blood supply; the addition of folic acid to the food supply to prevent congenital birth defects; and the MEDWatch program for reporting adverse events and product problems involving both drugs and devices. I created an Office of Criminal Investigation within the Agency to investigate suspected criminal violations of the Act, FDA regulations and other related laws. I also testified before a Congressional Committee regarding the risks of compounded pharmaceutical products, in 1996.

6. I am a senior advisor to TPG Capital, a leading global private equity firm, which owns pharmaceutical and biomedical companies. I served on the board of Aptalis Pharma and currently serve on the boards of Tokai Pharmaceuticals and the medical device and biologics company Immucor, Inc. In these advisory and fiduciary capacities, I have advised companies on the standards and duties of care within the pharmaceutical and medical device industry. I also chair the quality committee of Immucor and chaired the compliance committee of Aptalis, which involved ensuring compliance with FDA laws and requirements.

7. I was medical director of the Hospital of the Albert Einstein College of Medicine in the Bronx, New York prior to becoming FDA Commissioner. My responsibilities included medical oversight of pharmacy services including the formulary and Pharmacy and Therapeutics Committee.

8. It is my understanding that the current matter, *In re: New England Compounding Pharmacy, Inc. Products Liability Litigation*, MDL No. 2419 (D. Mass) involves the

following causes of action: Tennessee Products Liability Act of 1978, Tenn. Code Ann. § 29-28-101, et seq; Tennessee Health Care Liability Act ("THCLA"), Tenn. Code Ann. § 29-26-101 et seq; and various agency, respondeat superior, and other vicarious liability theories. The plaintiffs and defendants are listed in Schedule 1. It is my further understanding that plaintiffs allege that defendants purchased methylprednisolone acetate (MPA) manufactured by NECC, a compounding pharmacy, and that plaintiffs suffered from meningitis due to defendants' use of MPA from NECC for plaintiffs' epidural steroid injections (ESI).

9. I have been asked to provide testimony regarding FDA's policies concerning the traditional role of pharmaceutical compounding, as opposed to non-traditional pharmaceutical compounding; the risks of non-traditional pharmaceutical compounding that were considered and communications made by FDA regarding such risks, during and after my tenure as FDA Commissioner; the history of FDA's efforts to regulate the non-traditional compounding pharmaceutical industry, and the industry's resistance to such efforts; limitations on FDA's ability and resources to regulate nontraditional compounding; FDA and industry standards as to valid prescribing practices for compounded pharmaceuticals; and the role of a formulary system in promoting patient safety.

II. FDA'S REGULATION OF COMPOUNDED DRUGS

10. FDA has long regarded traditional pharmacy compounds as the mixing, combining or altering of ingredients by a licensed pharmacist in response to a prescription by practitioner for a particular patient. FDA has recognized the importance of compounding as meeting a specific need tailored to a patient's special medical needs. (See, Statement of Margaret A. Hamburg, M.D. Commissioner of Food and Drugs, Food and Drug

Administration, Department of Health and Human Services, Before the Subcommittee on Oversight and Investigations, House Committee on Energy and Commerce, U.S. House of Representatives, April 16, 2013 at p. 6.)[1]

11. In 1992, FDA stated in a Compliance Policy Guide 7132.16: "This Compliance Policy Guide (CPG) reflects long standing FDA policy that has been articulated in related CPGs, warning letters, and federal court decisions. FDA recognizes that pharmacists traditionally have extemporaneously compounded and manipulated reasonably quantities of drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner. This traditional activity is not the subject of this CPG." (*Id*., at 1).

12. Examples of compounding that FDA has recognized as meeting a patient need include reformulating a drug without a dye or a preservative in a patient who has an allergy to such dye or preservative. (Hamburg Statement, April 16, 2013, at 6).

13. Another example involves dispensing an alternative dosage form to meet the specific needs of a child or an elderly who cannot swallow commercially available tablets. (*Id.*; *See also* Sellers, et al., Pharmacy Compounding Primer for Physicians, Drugs 2012; 72:2043 at 2044).

14. Personally, I have asked a pharmacy to compound a drug for a specific child when the mixture of ingredients was not commercially available.

15. FDA has long recognized that pharmacists engaging in traditional compounding provide an important service.

[1] See Schedule 4, re Federal and State Regulation of Compounding Pharmacies.

16. I can personally attest that in the early 1990s FDA became concerned that certain pharmacies had begun producing drugs beyond what was considered traditional compounding.

17. In response to concerns about the safety of compounded drugs, FDA under my leadership issued a Compliance Policy Guide (CPG), initially numbered as Section 7132.16 and renumbered subsequently as 460.200. FDA in this policy guide set out FDA's enforcement policy on pharmacy compounding. The CPG described factors that the agency would consider in its decision-making regarding whether such compounded drugs were shipped in interstate commerce in violation of the federal Food, Drug & Cosmetic Act.

18. CPG 7132.16 stated: "FDA recognizes that a licensed pharmacist may compound drugs extemporaneously after receipt of a valid prescription for an individual patient (i.e., an oral or written order of a practitioner licensed by state law to administer or order the administration of the drug to an individual patient identified and treated by the practitioner in the course of his or her professional practice.) Pharmacies that do not otherwise engage in practices that extend beyond the limits set forth in this CPG may prepare drugs in very limited quantities before receiving a valid prescription, provided they can document a history of receiving valid prescriptions that have been generated solely within an established professional practitioner-patient-pharmacy relationship, and provided further that they maintain the prescription on file for all such products dispensed at the pharmacy as required by state law." (*Id.*, at 3-4).

19. CPG 7132.16 also stated, "In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an

FDA-approved drug that is commercially available. In these circumstances, patient-by-patient consultation between physician and pharmacist must result in documentation that substantiates the medical need for the variation of the compound. Pharmacies may not, without losing their status as retail entities, compound, provide, and dispense drugs to third parties for resale to individual patients. FDA will generally continue to defer to state and local officials regulation of the day-to-day practice of retail pharmacy and related activities. FDA anticipates that cooperative efforts between the states and the agency will result in coordinated investigations, referrals, and follow-up actions by the states. FDA may, in the exercise of its enforcement discretion, initiate federal enforcement actions against entities and responsible persons when the scope and nature of a pharmacy's activity raises the kinds of concerns normally associated with a manufacturer and that results in significant violations of the new drug, adulteration, or misbranding provisions of the [Food, Drug, and Cosmetic] Act. In determining whether to initiate such an action, the agency will consider whether the pharmacy engages in any of the following acts: … 2. Compounding, regularly, or in inordinate amounts, drug products that are commercially available in the marketplace and that are essentially generic copies of commercially available, FDA-approved drug products. … 5. Using commercial scale manufacturing or testing equipment for compounding drug products. 6. Compounding inordinate amounts of drugs in anticipation of receiving prescriptions in relation to the amounts of drugs compounded after receiving valid prescriptions. 7. Offering compounded drug products at wholesale to other state licensed persons or entities for resale. 8. Distributing inordinate amounts of compounded products out of

state. 9. Failing to operate in conformance with applicable state law regulating the practice of pharmacy." (*Id*., at 3-5).

20. CPG 7132.16 further stated, "Pharmacies engaged in promotion and other activities analogous to manufacturing and distributing drugs for human use are subject to the same provisions of the Act as manufacturers. District officers are encouraged to consult with state regulatory authorities to assure coherent application of this CPG to establishments which are operating outside of the traditional practice of pharmacy. FDA-initiated regulatory action may include issuing a warning letter, seizure, injunction, and/or prosecution. Charges may include, but need not be limited to, violations of 21 U.S.C. Sections 351(a)(2)(B), 352(a), 352 (f)(1), 352(o), and 355(a) of the Act." (*Id.*, at 6).

21. The compounding industry objected to FDA's approach and sought "to limit FDA's oversight of compounding." (Hamburg Testimony, April 16, 2013, at 7).

22. In 1997, Congress passed the Food and Drug Administration Modernization Act (FDAMA) of 1997 that became public law 105-115.

23. Congress enacted Section 503A of FDAMA to address FDA's authority regarding compounded drugs. The provisions of Section 503A exempted compounded drugs from 1) the pre-market approval requirements, 2) good manufacturing practice standards and 3) adequate directions for use, "if the drug product is compounded for an identified individual patient based on the unsolicited receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient, if the drug product meets the requirements of this section, and if the compounding:

"(I) is by—

(A) a licensed pharmacist in a State licensed pharmacy or a Federal facility, or

(B) a licensed physician, on the prescription order for such individual patient made by a licensed physician or other licensed practitioner authorized by State law to prescribe drugs; or

(2) (A) is by a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient; and

(B) is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the drug product, which orders have been generated solely within an established relationship between--

(i) the licensed pharmacist or licensed physician; and

(ii) (I) such individual patient for whom the prescription order will be provided; or

(II) the physician or other licensed practitioner who will write such prescription order."

24. These congressional provisions were subject to court challenges which, according to FDA, "produced conflicting case law and amplified the perceived gaps and ambiguity associated with FDA's enforcement authority over compounding pharmacies." (Hamburg Statement, April 16, 2013, at 7.)

25. The United States Supreme Court invalidated the advertising provisions of Section 503A. *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002).[2] That case was decided on April 29, 2002.

26. Promptly after the *Thompson v. Western States Medical Center* decision, FDA issued a revised compliance policy guide on compounded drugs, CPG 460.200; the CPG stated, "Issued: 3/16/1992 [referring to the earlier CPG 7132.16]; Reissued: 5/29/2002."

27. The 2002 update, CPG 460.200, retained the following statement from the predecessor CPG, 7132.16: "FDA recognizes that pharmacists traditionally have extemporaneously

[2] "Several non-speech-related means of drawing a line between compounding and large-scale manufacturing might be possible here. First, it seems that the Government could use the very factors the FDA relied on to distinguish compounding from manufacturing in its 1992 [Compliance Policy] Guide. For example, the Government could ban the use of 'commercial scale manufacturing or testing equipment for compounding drug products.' Guide, App. to Pet. for Cert. 76a. It could prohibit pharmacists from compounding more drugs in anticipation of receiving prescriptions than in response to prescriptions already received. *See ibid.* It could prohibit pharmacists from '[o]ffering compounded drugs at wholesale to other state licensed persons or commercial entities for resale.' *Id.,* at 77a. Alternately, it could limit the amount of compounded drugs, either by volume or by numbers of prescriptions, that a given pharmacist or pharmacy sells out of state. *See ibid." Thompson v. Western States Medical Center*, 535 U.S. at 372.

compounded and manipulated reasonably quantities of drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner. This traditional activity is not the subject of this CPG." (*Id.*, at 2).

28. CPG 460.200 stated, "when the scope and nature of a pharmacy's activities raise the kinds of concerns normally associated with a drug manufacturer and result in significant violations of the new drug, adulteration, or misbranding provisions of the Act, FDA has determined that it should seriously consider enforcement action. In determining whether to initiate such an action, the Agency will consider whether the pharmacy engages in any of the following acts: 1. Compounding drugs in anticipation of receiving prescriptions, except in very limited quantities in relation to the amounts of drugs compounded after receiving valid prescriptions. … 6. Using commercial scale manufacturing or testing equipment for compounding drug products. 7. Compounding drugs for third parties who resell to individual patients or offering compounded drug products at wholesale to other state licensed persons or commercial entities for resale. 8. Compounding drug products that are commercially available in the marketplace or that are essentially copies of commercially available FDA-approved drug products. In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an FDA-approved drug that is commercially available. In these circumstances, FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient." (*Id.*, at 3-4).

29. Additional legal challenges and court decisions ensued. See e.g. *Medical Center Pharmacy v. Mukasey*, 536 F. 3d 383 (5th Cir. 2008); Hamburg Statement, April 16, 2013, at 7)

30. FDA had begun work on issuing another compliance policy guide before the fungal meningitis outbreak occurred in 2012.[3]

31. Prior to 2013, while the validity of Section 503A was in doubt, the federal Food, Drug & Cosmetic Act's new drug provisions, good manufacturing provisions and adequate drug provisions were in effect.

32. In 2013, Congress enacted the Drug Quality and Security Act (DQSA), which provides a regulatory framework for pharmacy compounding practices.[4]

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[3] Hamburg Statement, April 16, 2013, at 8.

[4] The Drug Quality and Security Act enacted revised section 503A and new section 503B. The DSQA "reenacts Section 503A with the advertising provisions removed." Outterson, "The Drug Quality and Security Act—Mind the Gaps." New England Journal of Medicine 2014; DOI:10.1056/NEJMp1314691. Section 503B "creates an optional new license for sterile compounders, to be known as 'outsourcing facilities.'" *Id.* Revised section 503A stated:

"(a) In general

Sections 351 (a)(2)(B), 352 (f)(1), and 355 of this title shall not apply to a drug product if the drug product is compounded for an identified individual patient based on the receipt of a valid prescription order or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient, if the drug product meets the requirements of this section, and if the compounding—

"(1) is by—

(A) a licensed pharmacist in a State licensed pharmacy or a Federal facility, or

(B) a licensed physician, on the prescription order for such individual patient made by a licensed physician or other licensed practitioner authorized by State law to prescribe drugs; or

"(2) (A) is by a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient; and

(B) is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the drug product, which orders have been generated solely within an established relationship between—

(i) the licensed pharmacist or licensed physician; and

(ii) (I) such individual patient for whom the prescription order will be provided; or

(II) the physician or other licensed practitioner who will write such prescription order.

"(b) Compounded drug

(1) Licensed pharmacist and licensed physician

A drug product may be compounded under subsection (a) of this section if the licensed pharmacist or licensed physician—

…

(D) does not compound regularly or in inordinate amounts (as defined by the Secretary) any drug products that are essentially copies of a commercially available drug product.

(2) Definition

"For purposes of paragraph (1)(D), the term 'essentially a copy of a commercially available drug product' does not include a drug product in which there is a change, made for an identified individual patient, which produces for that patient a significant difference, as determined by the prescribing practitioner, between the compounded drug and the comparable commercially available drug product.

33. Under all versions of FDA's compliance policy guides through 2012, regardless of whether 503A was in effect, the FDA stated that compounding pharmacies that were not subject to FDA enforcement were those pharmacies that "traditionally have extemporaneously compounded and manipulated reasonably quantities of drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner." (CPG 7132.16 at p. 1; CPG 460.200, at 2.)

34. Throughout this period FDA supported its long-standing policy that compounding should be performed in a licensed pharmacy, by a licensed pharmacist, and that there must be a medical need for the compounded drug for an individual patient.

35. FDA has long recognized that non-traditional compounding poses higher risk than traditional compounding.[5]

36. FDA has also stated that there are certain compounded products that are not appropriate for compounding except under limited circumstances. These include drugs that are copies of FDA-approved drugs. "In determining whether to initiate [enforcement] action, the Agency will consider whether the pharmacy engages in any of the following acts: . . . 2. Compounding, regularly, or in inordinate amounts, drug products that are commercially available in the marketplace and that are essentially generic copies of commercially available, FDA-approved drug products." (CPG 460.200, p.4 para.8).[6]

Section 503B provides, "Sections 502(f)(1), 505, and 582 shall not apply to a drug compounded by or under the direct supervision of a licensed pharmacist in a facility that elects to register as an outsourcing facility if each of the following conditions is met: (1) Registration and Reporting.—The drug is compounded in an outsourcing facility that is in compliance with the requirements of subsection (b)" [relating to registration, inspection and adverse event reporting.]

[5] *See, e.g.,* "2006 Limited FDA Survey of Compounded Drug Products;" "The Special Risks of Pharmacy Compounding," FDA Consumer Health Information, May 31, 2007.

[6] FDA in CPG 460.200 did state "In certain circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an FDA-approved drug that is commercially available. In these circumstances, FDA will consider whether there is documentation of the medical need for the particular variation of the compound for the particular patient." *Id.*, at 4. FDA in CPG 7132.16 stated, "In certain

37. Compounded drugs are not generic drugs. Generic drugs are subject to FDA regulation under the abbreviated new drug application statutes and regulations.

38. FDA has over the decades involved itself in drug shortages. For example, FDA reacts to drug shortages by addressing underlying causes to increase product availability. *See* http://www.fda.gov/Drugs/DrugSafety/DrugShortages/ucm050796.htm#q4.[7]

39. In addition to federal regulation there is also state legislation that governs drug compounding.[8] In addition, health care institutions such as hospitals and outpatient clinics have policies intended to assure safe and appropriate procurement and use of medications.[9]

III. NON-TRADITIONAL COMPOUNDING PRODUCTS POSE A HIGHER RISK FOR THE PATIENTS

40. As I have testified, I and FDA have had long-standing concern about compounding of drugs that in essence is not aimed at meeting an individual patient's need but rather equivalent to larger scale manufacturing.

41. I and FDA have had long-standing concerns about a "shadow industry of unapproved generic drugs" developing. (Prepared Statement of David A. Kessler, M.D. Commissioner of Food and Drugs, Dept. of Health and Human Services, before the

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circumstances, it may be appropriate for a pharmacist to compound a small quantity of a drug that is only slightly different than an FDA-approved drug that is commercially available. In these circumstances, patient-by-patient consultation between physician and pharmacist must result in documentation that substantiates the medical need for the variation of the compound." *Id*., at 4.

[7] "FDA responds to potential drug shortages by taking actions to address their underlying causes and to enhance product availability. FDA determines how best to address each shortage situation based on its cause and the public health risk associated with the shortage. For manufacturing/quality problems, FDA works with the firm to address the issues. Problems may involve very low risk (e.g. wrong expiration date on package) to high risk (particulate in product or sterility issues). Regulatory discretion may be employed to address shortages to mitigate any significant risk to patients. FDA also works with other firms making the drugs that are in shortage to help them ramp up production if they are willing to do so. Often they need new production lines approved or need new raw material sources approved to help increase supplies. FDA can and does expedite review of these to help resolve shortages of medically necessary drugs. FDA can't require the other firms to increase production." Regarding drug shortages see Schedules 2 and 3.

[8] See Schedule 4 regarding federal and state regulation of compounding pharmacies.

[9] See Sections V and VI, below.

House Committee on Commerce, Subcommittee on Health and Environment, May 1, 1996).

42. Large scale manufacturing of drugs would, as I have testified, allow potentially dangerous drugs to be sold.

43. As I have testified, for example, sterile drugs could be compounded (even on a large scale) without regard to current good manufacturing practices (cGMPs) for sterile products. Improperly compounded sterile products could result in serious adverse effects, including death. (*Id.*)

44. By requiring prescriptions for each individual compounded drugs FDA limited the number of patients that could be harmed if a dangerous batch of drugs were made. While FDA guidelines allowed very limited batches to be made in anticipation of prescriptions, such limitations also sought to assure that compounded pharmacies were not bulk manufacturers that could expose a significant number of patients to needless risk.

45. Moreover, by requiring prescriptions for individual compounded drugs, FDA sought to assure that physicians made an individual risk benefit decision for a particular patient at a particular point in time, including that patient's medical need for a product that was not commercially available.

46. On December 13, 2002, the Centers for Disease Control and Prevention in its "Morbidity and Mortality Weekly Report" stated "This report describes five cases of fungal infection associated with contaminated drugs prepared at a compounding pharmacy. ("*Exophiala* Infection from Contaminated Injectable Steroids Prepared by a Compounding Pharmacy-United States, July-November 2002," MMWR 2002: 51: 1109-1112, at 1109.)

47. In 2006, FDA released "2006 Limited FDA Survey of Compounded Drug Products." In its document, FDA stated "[s]everal studies, including a survey conducted by FDA in 2001, have reported quality problems with various pharmacy-compounded drugs, including sub-potency, super-potency and contamination." To explore these quality issues, FDA conducted an additional survey of compounded drug products in 2006. FDA observed a variety of quality problems in the compounded drugs in its study. FDA concluded that "[p]oor quality compounded drugs are a serious public health concern, as improperly compounded products have been linked to grave adverse events, including deaths."

48. On May 31, 2007, FDA issued the FDA Consumer Health Information article "The Special Risks of Pharmacy Compounding." In this article FDA reported that more than 200 adverse events involving 71 compounded products had occurred since 1990. A number of the patients receiving contaminated compounded drugs suffered serious illnesses and death. FDA expressed its concern that some compounding pharmacies were acting outside of the bounds of traditional compounders including by making "large amounts of compounded drugs that are copies or near copies of FDA-approved commercially available drugs."

49. An article by Staes, et al., "Description of Outbreaks of Healthcare -Associated Infections Related to Compounding Pharmacies, 2000-2012," stated, "Between 2000 and prior to the 2012 fungal meningitis outbreak, 11 infectious outbreaks from contaminated compounded drugs were reported involving 207 case-patients with 17 deaths (8.2% case fatality rate)." Table 1, "Description of Outbreaks Associated with Contaminated Drugs Produced by Compounding Pharmacies Outside the Hospital Setting, Jan. 2000 - Nov.

2012," includes "methylprednisolone suspension for epidural injection," resulting in "Meningitis n=4 (1 died);" and "septic arthritis (n=2)."[10]

50. Martin Kelvas, Director of Pharmacy, for the non-profit St. Thomas Hospital and its clinics, testified that "compounding pharmacies served a purpose of being able to make a product that was not available, usually, had to be made for this patient, one patient at a time, specific for that use and was used pretty much immediately. (Kelvas Tr., 78:1-24) Mr. Kelvas testified that it would be "out of step within the industry or the standards within the industry to be bulk ordering MPA" from a compounding pharmacy, and that "if you're going to buy in bulk without patient-specific prescriptions, you still require the manufacturing license." (*Id.*, at 79:7-80:15; 156:4-10). Mr. Kelvas testified that compounding pharmacies were "not meeting the same standards as an FDA manufacturing plant," (*Id*., at 158:9-159:10). "Q. And one of the concerns about a compounding pharmacy acting as a manufacturer and doing bulk production is that they don't have that level of oversight from the FDA; correct? A. That is correct." (*Id*., at 159:20-24).

51. In my opinion, non-traditional compounded drugs pose a health risk for patients. Sterile non-traditional injectable compounded drugs pose a significant health risk for patients.

[10] This article cites a 2011 infectious episode with "bevacizumab intravitreal injection (preservative free)", resulting in endophthalmitis (permanent vision loss; 7 patients had globe loss). Total number of cases 12. The FDA issued an alert about 12 cases centered in Miami. *See* www.fda.gov/Drugs/DrugSafety/ucm270296.htm. The New York Times reported that outbreaks occurred in both Tennessee and in Florida for a total of 16 cases. (NYTimes, "Avastin injections are reported to cause blindness," http://www.nytimes.com/2011/08/31/health/31drug.html?_r=0; Tennessean, "Medicare may pick cheaper eye med Avastin," 2011 WLNR 18590981, 9/19/11.

IV. PRACTICAL IMPLICATIONS OF FDA'S LIMITED AUTHORITY OVER COMPOUNDED DRUGS

52. In light of the complexity of the regulatory framework for compounded pharmacies over the years, FDA has had limited ability to police all compounding of all compounded products.

53. Even with full regulatory authority no FDA inspector can be in every compounding pharmacy all the time.

54. As stated in the July 2013 Government Accountability Office (GAO) Report, at p. 13, "Drug Compounding: Clear Authority and More Reliable Data Needed to Strengthen FDA Oversight: "FDA lacks reliable information on entities that compound drugs, the types of drugs being compounded, and adverse events related to compounded drugs. Until 2013, FDA limited its inspections of compounding pharmacies to those conducted in response to complaints or adverse events, called 'for cause' inspections; however, the agency has recently conducted inspections of compounding pharmacies that were known to produce 'high-risk' sterile compounded drugs, and identified serious problems."[11]

55. FDA's regulatory framework for compounded pharmacy involves complementary oversight by state pharmacy boards and health departments.

V. EVEN WITH FDA AND STATE OVERSIGHT OF COMPOUNDED PHARMACY, PRACTITIONERS AND PROVIDERS HAVE RESPONSIBILITIES TO FOLLOW BASIC SAFETY PRACTICES.

56. Basic safety practices for healthcare providers include writing prescriptions in an appropriate manner for individual patients.

[11] FDA's resource constraints also impose limitations on its ability to oversee the regulation of compounded drugs. The Institute of Medicine (IOM), in its 2007 report titled, "The Future of Drug Safety: Promoting and Protecting the Health of the Public," has stated that, "the drug safety system is impaired by the following factors: serious resource constraints that weaken the quality and quantity of the science that is brought to bear on drug safety; an organizational culture in CDER that is not optimally functional; and unclear and insufficient regulatory authorities particularly with respect to enforcement." (*Id.,* at 4). The same report also cites FDA's "overextended human and financial resources." (*Id.*, at 67). These limitations are amplified in the context of compounded drugs.

57. An NECC "General Overview of Policies and Procedures for Compounding Sterile Products" states "NECC operates in accordance with the following general guidelines when compounding sterile products." The document goes on to state "Product is dispensed by patient-specific prescription only. There must be a specific practitioner-patient-pharmacist relationship to dispense to an individual patient or facility." (emphasis added)[12] STOPNC_0521 and 0522 (Schamberg Exhibit 31).

58. As noted above, CPG 7132.16 states, "Pharmacies that do not otherwise engage in practices that extend beyond the limits set forth in this CPG may prepare drugs in very limited quantities before receiving a valid prescription, provided they can document a history of receiving valid prescriptions that have been generated solely within an established professional practitioner-patient-pharmacy relationship, and provided further that they maintain the prescription on file for all such products dispensed at the pharmacy as required by state law" (emphasis added).

59. *The Art, Science, and Technology of Pharmaceutical Compounding*, by Lloyd Allen, Jr., Ph.D (4th Ed., 2012), states: "*Compounding* is the act of preparing, mixing or assembling a drug or device as the result of a practitioner's prescription drug order or initiative based on the practitioner-patient-pharmacist relationship in the course of professional practice, or for the purpose of, or incident to, research, teaching, or chemical analysis and not for sale or dispensing. *Compounding* also includes the preparation of drugs or devices in anticipation of prescription drug orders, on the basis of routine, regularly observed prescribing patterns. … Pharmacists may compound drugs in limited quantities prior to receiving a valid prescription, on the basis of a history of receiving valid prescriptions

[12] See Schedule 5 re Regulatory History of NECC. Schedule 5 is based on publicly available documents on the FDA.gov and Mass.gov websites. I have not been privy to internal FDA or state agency documents concerning review of NECC's conduct.

that have been generated solely within an established pharmacist-patient-prescriber relationship, and provided that the prescriptions are maintained on file for all such preparations dispensed at the pharmacy." (*Id.,* at 2; emphasis added).

60. Terry A. Grinder, a pharmacist investigator for the Tennessee Board of Pharmacy, testified: "Manufacturers, of course, would be under FDA jurisdiction, and they would be manufacturing bulk products; whereas a compounding pharmacy typically would be compounding a patient-specific product based on a patient—a prescriber-patient-pharmacy triad."[13] (emphasis added).

61. In my opinion, based on the above, a reasonable and prudent healthcare provider when utilizing compounded drugs would assure that 1) there is a patient specific prescription, 2) the name on the prescription reflects the name for whom the drug was intended, 3) the name on the prescription is a real not a fake or made up name, and 4) the prescription is generated solely within an established professional practitioner-patient-pharmacy relationship.[14]

62. In my opinion, making up names to obtain compounded drugs removes the FDA safeguard that physicians make an individual risk benefit decision for a particular patient at a particular point in time when prescribing compounded drugs.

[13] Grinder transcript at 17:2-4.

[14] I asked to review prescription order forms for MPA at St. Thomas Outpatient Neurosurgical Center. The prescription order forms that I have seen do not have any patient names on them. Schamberg Ex. 39, pp. STOPNC_0056-59,65-67, 70, 72-78, 80-81). I have seen a printout of names with the heading List Daily Chrt Pull which included "Mickey Mouse." *Id.*, pp. STOPNC_0060-64.

VI. REGULATORY DISTINCTIONS AMONG BRAND NAME, GENERIC AND COMPOUNDED DRUGS ON INSTITUTIONAL FORMULARIES

63. As noted above, in addition to federal and state regulations, health care institutions such as hospitals and outpatient clinics have policies intended to assure safe and appropriate procurement and use of medications.

64. As stated by the American Society of Health-System Pharmacists, "A *formulary system* is the ongoing process through which a health care organization establishes policies regarding the use of drugs, therapies, and drug-related products and identifies those that are most medically appropriate and cost-effective to best serve the health interests of a given patient population." American Society of Health-System Pharmacists. ASHP Guidelines on the Pharmacy and Therapeutics Committee and the Formulary System. *Am J Health-Syst Pharm.* 2008; 65:1272–83 (emphasis in original).

65. The "Rules and Regulations" of the St. Thomas Outpatient Neurosurgical Center state "All drugs and medications administered to Patients shall be those listed in the center formulary as approved by the Center's Medical Staff." (Schamberg Exhibit 41, at STOPNC-006761). In deposition testimony, Debra Schamberg stated:

Q. (By Mr. Nolan) Let's try that again. Exhibit 41 at Bates number STOPNC_6758, can you tell us what this is.
A. This is the medical staff rules and regulations for the St. Thomas Outpatient
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Neurosurgical Center.
Q. All right. Have you seen this document before?
A. In the past, I have, I'm sure.
Q. All right. And what's the purpose of having rules and regulations like this?
A. It's a guideline to go by.
Q. And is following the guidelines like this important to patient safety?
A. Yes.

11 Q. And is following written formularies, in
12 your view, important to patient safety?
13 A. Yes.[15]

66. The St. Thomas Outpatient Neurosurgical Center formulary (Schamberg Exhibit 40) lists the following at page STOPNC_0537, under the heading, "Corticosteroids:":[16]

Decadron	4mg/ml, 1ml vial.
Depomedrol	80mg/ml, 1ml vial
Solumedrol	125mg/2ml vial
Celestone Soluspan	30mg/5ml vial

67. FDA reviews the proprietary name (brand) of prescription drug products. New drug applications relate to a specific proprietary name drug. The new drug application for a specific proprietary name drug relates to the specific drug manufactured by a specific drug company.

68. Depo-Medrol refers to the drug manufactured by Pfizer subject to NDA number 011757 that was approved on May 28, 1959.[17]

69. Methylprednisolone acetate is the generic name that was subject to an abbreviated new drug application (ANDA) approved by the FDA and manufactured by Sandoz and Teva Pharmaceuticals USA.[18]

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[15] Schamberg Tr., at 181:21-182:13.

[16] See Schedule re Statements and Articles by FDA Employees and FDA Advisors regarding Epidural Steroid Injections and Industry Responses.

[17] According to the FDA's National Drug Code Directory, the original NDA for Depo-Medrol in 1959 was registered to "Pharmacia and Upjohn Company." http://www.accessdata.fda.gov/scripts/cder/ndc/dsp_searchresult.cfm. "Pfizer Inc and Pharmacia Corporation began operating as a unified company on April 16, 2003." http://www.pfizer.com/about/history/pfizer_pharmacia

[18] "Teva Pharmaceutical Industries Ltd. (NASDAQ: TEVA) announced today that the U.S. Food and Drug Administration has granted final approval for the Company's ANDA for Methylprednisolone Acetate Injectable Suspension, 40 mg/mL and 80 mg/mL in single dose vials. Teva's Methylprednisolone Acetate Injectable Suspension is the AP-rated generic equivalent of Pfizer's Depo-Medrol® Injection, an anti-inflammatory glucocorticoid for intramuscular, intrasynovial, soft tissue or intralesional injection.." http://ir.tevapharm.com/phoenix.zhtml?c=73925&p=irol-newsArticle&ID=1557135. Sandoz' ANDA for

70. FDA has, by approving the ANDA, determined that Depo-Medrol and methylprednisolone acetate are bioequivalent. The manufacturing processes may differ for the two drugs as they are manufactured by different drug companies. Both the brand name and the generic products are manufactured under good manufacturing practices[19] pursuant to FDA regulations.

71. The St. Thomas Outpatient Neurosurgical Center formulary lists Depo-Medrol 80mg. Depo-Medrol refers to the drug manufactured by Pfizer subject to NDA number 011757 that was approved on May 28, 1959.

72. Compounded methylprednisolone acetate was neither approved under a new drug application (brand) nor an abbreviated new drug application (generic) nor is it listed in the St. Thomas Outpatient Neurosurgical Center formulary.

VII. CONCLUSIONS

Based on the above, in my opinion:[20]

73. Pharmacists traditionally have extemporaneously compounded and manipulated reasonably quantities of drugs upon receipt of a valid prescription for an individually identified patient from a licensed practitioner, and pharmacists engaging in traditional compounding provide an important service.

74. Non-traditional compounded drugs pose a health risk for patients. Sterile non-traditional injectable compounded drugs pose a significant health risk for patients.

75. According to FDA and industry standards, basic safety practices for healthcare providers include writing prescriptions in an appropriate manner for individual patients.

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methylprednisolone acetate was approved on January 29, 2009.

[19] Good manufacturing practices allows for total quality improvement which included complaint analysis, monitoring, root cause detection, recalls and preventive controls. These processes allow for continuous quality improvement on the part of regulated drug manufacturers.

[20] This section is not meant as an all-inclusive list of all my opinions. Please see report for opinions.

76. According to FDA and industry standards, compounding pharmacies require a specific practitioner-patient-pharmacist relationship to dispense to an individual patient or facility.

77. A reasonable and prudent healthcare provider when utilizing compounded drugs would assure that 1) there is a patient specific prescription, 2) the name on the prescription reflects the name for whom the drug was intended, 3) the name on the prescription is a real not a fake or made up name, and 4) the prescription is generated solely within an established professional practitioner-patient-pharmacy relationship.

78. Making up names to obtain compounded drugs removes the FDA safeguard that physicians make an individual risk benefit decision for a particular patient at a particular point in time when prescribing compounded drugs.

79. A formulary system identifies those drugs that are most medically appropriate and cost-effective, to best serve the health interests of a given patient population, and following a written formulary is important to patient safety. Compounded methylprednisolone acetate was not listed in the St. Thomas Outpatient Neurosurgical Center formulary.

December 16, 2015

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